

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:** Please amend the claims as follows:

**Claim 1. (Currently Amended)** ~~Use of a neuturin product and/or a modulator/effector thereof for the manufacture of a medicament to stimulate and/or induce~~ A method for stimulating and/or inducing the differentiation of insulin producing cells from progenitor cells comprising contacting said progenitor cells with a neutrin product or a modulator thereof or an effector thereof.

**Claim 2. (Currently Amended)** ~~The use of~~ method according to claim 1, wherein the progenitor cells are stem cells.

**Claim 3. (Currently Amended)** ~~The use of~~ method according to claim 1, wherein the stem cells are embryonic or somatic stem cells.

**Claim 4. (Currently Amended)** ~~The use of~~ method according to Claim 1, wherein the stem cells are of mammalian origin, ~~preferably of human origin,~~ with the proviso that the use of human embryos is excluded.

**Claim 5. (Currently Amended)** ~~The use of~~ method according to Claim 1, wherein the progenitor cells have been transfected with a pancreatic gene, ~~particularly the Pax4 gene.~~

**Claim 6. (Currently Amended)** ~~The use of a neuturin product and/or a modulator/effector thereof for the manufacture of a medicament to promote the~~ A method for promoting protection, survival and/or regeneration of insulin producing cells comprising contacting said insulin producing cells with a neutrin product or a modulator thereof or an effector thereof.

**Claim 7. (Currently Amended)** ~~The use of~~ method according to claim 6, wherein the insulin producing cells are beta-cells.

**Claim 8. (Currently Amended)** ~~The use of~~ method according to claim 6, wherein the insulin producing cells are of mammalian origin, ~~preferably of human origin.~~

**Claim 9. (Currently Amended)** ~~The use of~~ method according to Claim 6, wherein the insulin

producing cells have been transfected with a pancreatic gene, particularly the Pax4 gene.

**Claim 10. (Currently Amended)** The ~~use of method according to~~ Claim 1 for the prevention or treatment of a disease going along with impaired beta-cell function.

**Claim 11. (Currently Amended)** The ~~use of method according to~~ claim 10 for the treatment of beta-cell degeneration in patients suffering from diabetes type I, LADA, or progressed diabetes type II.

**Claim 12. (Currently Amended)** The ~~use of method according to~~ claim 10 for the prevention of beta-cell degeneration in patients at risk to develop beta-cell degeneration, like for example but not limited to patients suffering from diabetes type I or II, or LADA in early stages.

**Claim 13. (Currently Amended)** The ~~use of method according to~~ Claim 1, wherein a neurturin product or a modulator/effector thereof that influences the expression level or function of a neurturin product is administered to a patient

- (i) as a pharmaceutical composition ~~e.g. enterally, parenterally or topically directly to the pancreas,~~
- (ii) via implantation of neurturin protein product expressing cells, and/or
- (iii) via gene therapy.

**Claim 14. (Currently Amended)** The ~~use of method according to~~ claim 13, wherein the neurturin product or modulator/effector thereof is administered in combination with another pharmaceutical composition useful to treat beta-cell degeneration, for example but not limited to hormones, growth factors, or immune modulating agents.

**Claim 15. (Currently Amended)** The ~~use of method according to~~ Claim 1, wherein the neurturin product is a protein including purified natural, synthetic or recombinant neurturin or a variant thereof ~~and variants thereof~~.

**Claim 16. (Currently Amended)** The ~~use of method according to~~ claim 15 wherein the variant comprises an ~~variants are selected from~~ insertion, substitution, deletion ~~variants and/or or a~~ chemically modified derivative ~~derivatives, for example but not limited to hybrids of neurturin and other TGF-beta proteins preferably from the GDNF-family.~~

**Claim 17. (Currently Amended)** The ~~use of method according to~~ claim 15, wherein the neurturin product is ~~selected from proteins or peptides~~ a protein or a peptide which is substantially homologous to

- (a) the human neurturin precursor protein having the amino acid sequence published as GenBank Accession Number NP\_004549 and/or ~~to~~
- (b) the mature neurturin protein product that results from the cleavage of the neurturin protein precursor published as GenBank Accession number NP\_004549.

**Claim 18. (Currently Amended)** The ~~use of method according to~~ Claim 1, wherein the neurturin product is a nucleic acid ~~which encodes; e.g. RNA and/or DNA encoding~~ a neurturin protein product.

**Claim 19. (Currently Amended)** The ~~use of method according to~~ Claim 1, wherein the neurturin product is ~~selected from neurturin homodimers or heterodimers~~ a neurturin homodimer or a heterodimer of a neurturin protein product and another protein, wherein the other protein ~~preferably belongs to~~ is a member of the GDNF-family or a nucleic acid coding therefor.

**Claim 20. (Currently Amended)** The ~~use of method according to~~ Claim 1, wherein the neurturin product is of mammalian origin, ~~preferably human origin.~~

**Claim 21. (Currently Amended)** The ~~use of method according to~~ Claim 1, wherein the differentiation of progenitor, ~~e.g. stem cells into insulin-producing~~ cells in vitro comprises

- a) optionally activating one or more pancreatic genes in progenitor cells,
- b) optionally aggregating said cells to form embryoid bodies,
- c) cultivating said cells or embryoid bodies in specific differentiation media containing neurturin protein product and
- d) identifying and optionally selecting insulin-producing cells.

**Claim 22. (Currently Amended)** The ~~use of method according to~~ claim 21, wherein the neurturin-treated insulin producing cells are

- (i) capable of a response to glucose and/or
- (ii) capable of expressing glucagon.

**Claim 23. (Currently Amended)** The ~~use of~~ method according to Claim 21, wherein the neurturin-treated insulin producing cells are capable of normalizing blood glucose levels after transplantation into mice.

**Claim 24. (Currently Amended)** The ~~use of~~ method according to Claim 1, wherein an effective amount of in vitro neurturin-treated cells are transplanted to a patient in need.

**Claim 25. (Currently Amended)** The ~~use of~~ method according to Claim 1, comprising a stimulation of neurturin expression, wherein cells from a patient in need that have been modified to produce and secrete a neurturin protein product in vitro are re-implanted into the patient and/or wherein cells of a patient in need are modified to produce and secrete a neurturin protein product in vivo.

**Claim 26. (Currently Amended)** The ~~use of~~ method according to Claim 1 in combination with at least one further other pharmaceutical agent.

**Claim 27. (Currently Amended)** The ~~use of~~ method according to claim 26 in combination with at least one further pharmaceutical agent suitable for the treatment or prevention of pancreatic diseases and/or obesity and/or metabolic syndrome.

**Claim 28. (Currently Amended)** The ~~use of~~ method according to claim 27 in combination with at least one further pharmaceutical agent suitable for stimulating and/or inducing the differentiation of insulin producing cells from progenitor cells.

**Claim 29. (Currently Amended)** The ~~use of~~ method according to claim 26 in combination with at least one further pharmaceutical agent which has an immunosuppressive activity.

**Claim 30. (Original)** A method for differentiating or regenerating cells into functional pancreatic cells, the method comprising: (a) cultivating cells capable of being differentiated or regenerated into pancreatic cells in the presence of an effective amount of neurturin in vitro (b) allowing the cells to develop, to differentiate and/or to regenerate at least one pancreatic function; and (c) optionally preparing an effective amount of the differentiated or regenerated pancreatic cells for transplantation into a patient in need thereof.

**Claim 31. (Currently Amended)** The method ~~of~~ according to claim 30, wherein the patient in need is a human individual.

**Claim 32. (Currently Amended)** The method ~~of~~ according to claim 30, wherein the patient in need has (a) functionally impaired, (b) reduced numbers and/or (c) functionally impaired and reduced numbers of pancreatic cells.

**Claim 33. (Currently Amended)** The method ~~of~~ according to Claim 30, wherein said patient in need is a type I diabetic patient or type II diabetic patient or LADA patient.

**Claim 34. (Currently Amended)** The method ~~of~~ according to Claim 30, wherein the pancreatic cells are insulin-producing cells.

**Claim 35. (Currently Amended)** The method ~~of~~ according to Claim 30, wherein the pancreatic cells are beta-cells of the pancreatic islets.

**Claim 36. (Currently Amended)** The method ~~of~~ according to Claim 30, wherein the cells in step (a) are selected from embryonic stem cells, adult stem cells, or somatic stem cells.

**Claim 37. (Currently Amended)** The method ~~of~~ according to Claim 31, wherein the cells in step (a) are of mammalian origin, preferably human origin, with the proviso that the use of human embryos is excluded.

**Claim 38. (Currently Amended)** The method ~~of~~ according to Claim 30, wherein neurturin is added at concentrations between 1 ng/ml and 500 ng/ml, ~~preferably between 10 and 100 ng/ml, more preferably at about 50 ng/ml.~~

**Claim 39. (Currently Amended)** The method ~~of~~ according to Claim 30, wherein the at least one pancreatic function is selected from insulin production in response to glucose and expression of glucagon.

**Claim 40. (Original)** A method for differentiating or regenerating cells into functional pancreatic cells, the method comprising: preparing an effective amount of a neurturin product or of cells capable of expressing a neurturin product for administration to a patient in need

thereof.

**Claim 41. (Currently Amended)** The method of ~~of~~ according to claim 40, wherein the neururin product is a neururin protein product.

**Claim 42. (Currently Amended)** The method of ~~of~~ according to claim 40, wherein the neururin product is a nucleic acid encoding a neururin protein product.

**Claim 43. (Currently Amended)** The method of ~~of~~ according to claim 40, wherein cells have been modified to produce and secrete a neururin protein product and are prepared for transplantation into a suitable location in the patient.

**Claim 44. (Withdrawn)** A cell preparation comprising neururin-treated functional pancreatic cells obtainable by the method of Claim 30.

**Claim 45. (Withdrawn)** A cell preparation comprising a neururin product expressing cells obtainable by the method of Claim 30.

**Claim 46. (Withdrawn)** The preparation of claim 44, which is a pharmaceutical composition.

**Claim 47. (Withdrawn)** The preparation of Claim 44 for the treatment or prevention of pancreatic diseases, particularly diabetes.

**Claim 48. (Withdrawn)** The preparation of Claim 44 for administration by transplantation or for use in a medical device.

**Claim 49. (Withdrawn)** The preparation of Claim 44, which contains pharmaceutically acceptable carriers, diluents, and/or additives.

**Claim 50. (Withdrawn)** The preparation of Claim 44, which is a diagnostic composition.

**Claim 51. (Withdrawn)** The preparation of Claim 44, which is a therapeutic

composition.

**Claim 52. (Withdrawn)** The preparation of Claim 44 for the manufacture of an agent for the regeneration of pancreatic tissues or cells, particularly pancreatic beta cells.

**Claim 53. (Withdrawn)** The preparation of Claim 44 for application in vivo.

**Claim 54. (Withdrawn)** The preparation of Claim 44 for application in vitro.

**Claim 55. (Withdrawn)** A method for identifying and/or characterizing compounds capable of modulating the differentiation or regeneration of cells into functional pancreatic, particularly insulin-producing cells comprising:

contacting a compound to be tested with cells under conditions wherein the cells are capable of being differentiated or regenerated into functional pancreatic cells in the presence of neurturin and

determining the effect of the compound on the differentiation process.

**Claim 56. (Withdrawn)** The method of claim 55 comprising transfecting the cells with a DNA construct containing a reporter gene under regulatory control of a gene involved in beta-cell differentiation, contacting said transfected cells with a compound to be tested and determining the activity of the reporter gene.

**Claim 57. (Withdrawn, Currently Amended)** The method of claim ~~54~~ 55 comprising contacting embryoid bodies which are cultivated in a differentiation medium enhancing beta-cell differentiation with a compound to be tested and determining differentiation into insulin-producing cells.

**Claim 58. (Withdrawn)** A method for identifying and/or characterizing compounds capable of modulating the differentiation or regeneration of cells into functional pancreatic, particularly insulin-producing cells comprising:

contacting a compound to be tested with cells under conditions wherein the cells are capable of being differentiated or regenerated into functional pancreatic cells and determining the effect of the compound on the expression of neurturin.

**Claim 59. (Withdrawn)** Use of a preparation of neurturin expressing cells for the

treatment and prevention of diabetes.

**Claim 60. (Withdrawn)** The use of claim 59 for inducing the regeneration of pancreatic cells.

**Claim 61. (Withdrawn)** The use of claim 60, wherein pancreatic cells are beta-cells of the islets.

**Claim 62. (Withdrawn)** Use of a preparation of neurturin-treated cells for the treatment and/or prevention of diabetes.

**Claim 63. (Withdrawn)** The use of claim 62 wherein the cells are differentiated progenitor cells capable of insulin production.

**Claim 64. (New)** The method according to Claim 4, wherein the stem cells are of human origin, with the proviso that the use of human embryos is excluded.

**Claim 65. (New)** The method according to Claim 5, wherein the progenitor cells have been transfected with a Pax4 gene.

**Claim 66. (New)** The method according to claim 8, wherein the insulin producing cells are of human origin.

**Claim 67. (New)** The method according to Claim 13, wherein the pharmaceutical composition is administered enterally, parenterally or topically directly to the pancreas.

**Claim 68. (New)** The method according to Claim 16, wherein the variant is a hybrid of neurturin or a TGF-beta protein from the GDNF-family.

**Claim 69. (New)** The method according to Claim 38, wherein neurturin is added at concentrations between 10 and 100 ng/ml.

**Claim 70. (New)** The method according to Claim 38, wherein neurturin is



added at a concentration of 50 ng/ml.